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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,407	12/08/2006	Takumi Teratani	701053	2167

23460 7590 09/29/2010

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,407	TERATANI ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/24/2010 has been entered.

Amended claims 8-12 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 102(b) as being anticipated by Loring, J. (WO 99/27076; IDS) was withdrawn in light of Applicant's amendment; particularly with the limitations ""consists essentially of the following steps (A)-(E) performed using a culture medium with 2% or less serum concentration" and "wherein a rat leukemia inhibitory factor (rLIF)-containing culture medium is used in steps (C)-(E).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 8-10 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loring, J. (WO 99/27076; IDS) in view of Price et al. (WO 98/30679; IDS) and Takahama et al. (Oncogene 16:3189-3196, 1998; IDS). ***This is a modified rejection necessitated by Applicant's amendment.***

It is noted that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps **and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention**. In re Herz, 537 F.2d 549, 551-52,190 USPQ 461, 463 (CCPA 1976) (emphasis in original). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, **absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."** See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as

constituting a material change in the basic and novel characteristics of the invention."). See also AK Steel Corp. v. Sollac, 344 F.3d 1234, 1240-41, 68 USPQ2d 1280, 1283-84 (Fed. Cir. 2003) (Applicant's statement in the specification that "silicon contents in the coating metal should not exceed about 0.5% by weight" along with a discussion of the deleterious effects of silicon provided basis to conclude that silicon in excess of 0.5% by weight would materially alter the basic and novel properties of the invention. Thus, "consisting essentially of" as recited in the preamble was interpreted to permit no more than 0.5% by weight of silicon in the aluminum coating.); In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). **If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention**.

Loring already disclosed at least a method for obtaining non-mouse embryonic stem cells, including rat embryonic stem cells, said method comprises: (a) culturing harvested blastocysts or delayed-blastocysts in individual wells of a 24-well plate in any appropriate medium under any conditions which allow for growth and proliferation of ES cells**, with an exemplified medium is DMEM with glutamine and high glucose supplemented with 15% fetal bovine serum, 1 X non-essential amino acids, 0.1 mM 2-mercaptoethanol and antibiotics**; (b) the inner cell mass (ICM) was removed under conditions that minimize contamination with other cell types after about 3 to 5 days in culture using a micropipette and then dissociated with 0.25% trypsin, under

which conditions the ICM is dispersed either to a single cell suspension or **more preferably to produce small groups of cells**; (c) ICM cultures were cultured in 6 well dishes and **colonies arising from the dispersed ICMs will be selected by morphology criteria** with exogenous growth factors (for example, bFGF, LIF and SCF) alone or in combination may be added to the cultures **or** ICM cultures were cultured on any feeder layer that is not necessarily limited to SNL 76/7 cells producing LIF, such as STO cells; (d) after about a week of culture, colonies that resembled ES cells were dissociated and sub-cultured; (e) the sub-cultured ES cells were passed once to obtain cell lines BNRB-1 and FRDB-1 which are AP positive; and (e) the rat cell lines were co-cultured with mouse ES cells to obtain pluripotent rat ES cells which differentiated into a number of morphologically different cell types and embryoid bodies, including the ability of making a transgenic rat (see at least the abstract; pages 11-14; particular example 2, page 26, lines 7-8; examples 4-6). Loring also disclose specifically that the co-culture method arises from the observations that mouse ES cells differentiate more easily and often when they were cultured at low density rather than high density (page 13, lines 24-27). **It is noted that in step (a), the exemplified medium for culturing harvested blastocysts or delayed-blastocysts does not contain any LIF (page 12, lines 17-22); and therefore this teaching meets the limitation of step (A) of amended claim 8**. Moreover, Loring also stated that "Culture medium (LIF; LIF and SCF, or LIF, SCF, and bFGF) made no apparent difference in the early blastocyst culture" (page 24, lines 15-16).

Loring does not teach specifically the use of a culture medium with 2% or less serum concentration, such as a culture medium comprising a serum replacement reagent, in steps (A)-(E); **and** the use of a rat LIF-containing culture medium in steps (C)-(E).

At the effective filing date of the present application, Price et al already taught the use of a serum replacement medium to support the growth of embryonic stem cells in culture to avoid many problems associated with the use of serum as well as time consuming pre-screening process of serum (see at least the abstract; Summary of the Invention, page 3, second and third paragraph; and examples).

Moreover, Takahama et al already cloned cDNA encoding a rat LIF and demonstrated that **culture supernatant of the rat LIF cDNA-transduced rat fibroblast cell line could maintain the stem-cell phenotype of rat ES cells which showed alkaline phosphatase activity, and this effect was much stronger than that by murine LIF** (see at least the abstract). Takahama et al specifically taught that the availability of rat LIF cDNA will assist the establishment of *in vitro* culture conditions of rat ES cells and maintaining these cells in an undifferentiated state (page 319, col. 1).

It would have been obvious for an ordinary skilled artisan to modify the method of Loring by also using a serum replacement medium for establishment of pluripotent rat embryonic stem cells in light of the teachings of Price et al; and also selecting and using specifically rat LIF in a culture medium for culturing primary rat embryonic stem cells obtained from a culture of dissociated inner cell mass, and subsequent sub-culture

steps for establishment of rat embryonic stem cells in light of the teachings of Takhama et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because the use of a serum replacement medium to support the growth of embryonic stem cells in culture avoids many problems associated with the use of serum as well as time consuming pre-screening process of serum as taught by Price et al; and that rat LIF has been shown by Takahama et al to be effective in maintaining the stem cell phenotype of rat ES cells which showed alkaline phosphatase activity, and its effect is much stronger than that of murine LIF.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Loring together with Price et al and Takahama et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Loring, J. (WO 99/27076; IDS) in view of Price et al. (WO 98/30679; IDS) and Takahama et al. (Oncogene 16:3189-3196, 1998; IDS) as applied to claims 8-10 and 12-13 above, and further in view of Vassilieva et al. (Experimental Cell Research 258:361-373, 2000; IDS) and Mandalam et al (US 7,297,539).

The combined teachings of Loring, Price et al and Takahama et al. were already presented above. However, none of the cited references teaches specifically the step of mechanically dissociating the primary embryonic stem cells for passaging.

At the effective filing date of the present application, in a method for establishment of SSEA-1- and Oct-4-expressing rat embryonic stem-like cell lines, Vassilieva et al already taught selecting and passaging colonies representing typical morphology of compacted ES cells were selected and passaged every day by mechanical disaggregation (see at least the abstract and particularly the section "Establishment of rat ES-like cell lines" on page 362 and col. 1 of page 363 and Table 1).

Additionally, at least in a method for growing human embryonic stem cells Mandalam et al also taught selecting individual ES cell colony by micropipette and/or ES cells are triturated with a pipette into clumps of adherent cells, about 10-2000 cells in size, which were then passaged into the new culture environment (see at least Summary of the Invention; and particularly col. 9, line 53 continues to line 3 of col. 10 and lines 48-63 in col. 10).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Loring, Price et al and Takahama et al. by also mechanically dissociating the primary embryonic stem cells for passaging in light of the teachings of Vassilieva et al and Mandalam et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because mechanically dissociating ES cells during cell passage has been

taught successfully in the preparation of rat and human ES stem cells by Vassilieva et al and Mandalam et al, respectively.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Loring, Price et al, Takahama et al, Vassilieva et al and Mandalam et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above obviousness rejections in the Amendment filed on 8/24/2010 (pages 5-8); along with the 1.132 Declaration of Takahiro Ochiya dated 11/16/09, have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that the instant amended claims exclude essential steps other than steps (A)-(E) due to the claim language "consisting essentially of"; and therefore none of the cited references teaches or suggests the method as claimed. With respect to the primary Loring reference, Applicants also argue that one of skilled in the art upon reading Loring (see, e.g., Example 2 and Example 5) would understand that the medium disclosed therein is a basal medium and that the culture media actually used for blastocyst culture are supplemented with (1) LIF, (2) LIF and SCF, or (3) LIF, SCF and bFGF; and therefore all of the culture media used for blastocyst culture in

Loring contain LIF which conflicts with the steps of the claimed invention. Applicants further argue that the Takahama reference discloses the use of (i) IGF-II and (ii) IGF-II and LIF containing media for establishing ES/EC cells and that IGF-II is essential for maintenance and growth of ES cells; but LIF-containing medium is always used for establishing ES cell-like colonies. Accordingly, based on the cited references that an ordinary skill in the art would believe that LIF was necessary for ICM formation in rat blastocysts; and that the present invention is based on the finding that the use of LIF-free medium for blastocyst culture results in an efficient ICM formation in rat blastocysts and enables rat ES cell establishment without co-culture with mouse ES cells as evidenced by the 1.132 Declaration of Takahiro Ochiya dated 11/16/09.

First, please noted that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps **and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention**. In re Herz, 537 F.2d 549, 551-52,190 USPQ 461, 463 (CCPA 1976) (emphasis in original). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, **absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."** See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention."). See also AK Steel Corp. v. Sollac, 344 F.3d 1234, 1240-41, 68 USPQ2d 1280, 1283-84

(Fed. Cir. 2003) (Applicant's statement in the specification that "silicon contents in the coating metal should not exceed about 0.5% by weight" along with a discussion of the deleterious effects of silicon provided basis to conclude that silicon in excess of 0.5% by weight would materially alter the basic and novel properties of the invention. Thus, "consisting essentially of" as recited in the preamble was interpreted to permit no more than 0.5% by weight of silicon in the aluminum coating.); In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). **If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention**. It should be noted that the additional co-culture step with mouse ES cells in the method of Loring renders the co-cultured non-mouse ES cells, including rat ES cells, to express and maintain markers of pluripotent ES cells and properties that are substantially similar to those of rat ES cells of the present invention. Moreover, it is noted that **the present invention involves the co-culture of rat blastocyst with inactivated feeder cells** (see at least all of the examples).

Second, Loring states **"The primary blastocysts from which the ES cells are derived are grown in any appropriate medium under any conditions which allow for growth and proliferation of the ES cells. For instance, one suitable medium is mouse ES medium (DMEM with glutamine and high glucose (Gibco) supplemented with 15% fetal bovine serum (FBS: HyClone), 1 X non-essential**

amino acids, 0.1 mM 2-mercaptoethanol, and antibiotics)" (page 12, lines 17-22). Clearly, Loring teaches using a medium without LIF as a supplement for culturing primary blastocysts as an embodiment of teachings. Additional, **please note that the teachings of Loring are not necessarily limited to exemplifications such as examples 2 and 5 which could be preferred embodiments**.

Third, it is noted that the Takahama reference does not disclose the use of (i) IGF-II and (ii) IGF-II and LIF containing media for establishing ES/EC cells and that IGF-II is essential for maintenance and growth of ES cells. **This teaching is found only in the JP 05-304951 (also see provided English translation, IDS), which is not part of the above 103 rejection**, disclosing the use of a culture broth comprises IGF-II **OR** IGF-II and LIF for establishing ES/EC cells, including rat ES cells (see translation at page 12, paragraph 16); and stated that "From theses results of comparative cultivation, it was found that IFG-II is essential for the maintenance and growth of ES cells" (see translation at page 17, last sentence of second last paragraph). **The JP 05-304951 was cited by the Examiner to indicate simply the state of the prior art; and once again the teachings of JP 05-304951 was not necessarily limited only to exemplifications**. Thus, at the effective filing date of the present application at least both Loring and JP 05-304951 taught explicitly that blastocysts can be cultured in a suitable medium that is with **or** without the presence of LIF. Furthermore, Yamanaka et al (Anim. Sci. 72:285-290, 2001) also taught that the presence of bLIF in culture medium has no effect on the cell number of inner cell mass (ICM) in cultured bovine embryos (see at least the abstract).

Fourth, the higher efficiency of forming inner cell masses in the absence of LIF as described in the 1.132 Declaration of Takahiro Ochiya is irrelevant because as already noted above Loring already taught the step of culturing harvested blastocysts or delayed-blastocysts in individual wells of a 24-well plate in any appropriate medium under any conditions which allow for growth and proliferation of ES cells, **with an exemplified medium is DMEM with glutamine and high glucose supplemented with 15% fetal bovine serum, 1 X non-essential amino acids, 0.1 mM 2-mercaptoethanol and antibiotics** (page 12, lines 18-22); or alternatively ICM cultures were cultured on any feeder layer that is not necessarily limited to SNL 76/7 cells producing LIF, such as STO cells which are not genetically engineered to produce LIF.

2. With respect to the issue of inconsistency between the data disclosed in the present invention and the data disclosed in Ueda et al, which is a post-filing reference by the inventors, specifically rat ES cells of the present invention are positive for alkaline phosphatase (Fig. 13), while the rat ES cells of Ueda et al are negative for alkaline phosphatase; Applicants note that this inconsistency is likely caused by the serum concentration contained in the culture medium (rat ES cells were cultured in serum-free medium in the present invention; while rat ES cells of Ueda et al were cultured in 3% FBS). The culture method disclosed in Ueda et al which uses 3% FBS culture medium, is not encompassed by the claimed invention.

It is noted that the instant specification defines the term “substantially serum free” means not to contain serum in an amount that rat ES cell loses the properties as an ES cell (e.g., becomes negative for alkaline phosphatase activity) due to the effect of

serum. Specifically, **it means the serum concentration is 10% or less, preferably 5% or less, more preferably 2% or less** (page 17, lines 15-28). Despite the absence of alkaline phosphatase expression in rat ES cells disclosed by Ueda et al, which is a post-filing reference by the present inventors, **the cells are still called rat ES cells** and they are capable of making chimera rats. Although, Applicants attributed the inconsistency with regard to the alkaline phophatase expression level between rat ES cells of the present invention and rat ES cells disclosed by Ueda et al is likely caused by the serum concentration (serum-free vs 3% FBS, respectively); it is noted the instant amended claims encompass the preparation of rat ES cells in the presence of 2% or less serum containing medium and there is no evidence of record indicating or suggesting that the presence of 2%, 1% or even 0.5% serum would not have similar effects as those of 3% serum (e.g., resulting in the preparation of rat cells which do not express alkaline phosphatase which is a marker of pluripotent ES cells).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633